Acute Hepatic Sequestration in Sickle Cell Disease

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Sickle cell anemia is a disease that affects one out of every 600 African Americans.[1] It is often debilitating and can cause many physical restrictions to individuals with the disease. The disease has many complications which can be vexing for patients and their physicians. The hepatic complications attributed to vascular occlusion encompass a variety of clinical syndromes of which the relationship among clinical presentation, biochemical findings, and histologic features remains unclear.[2] The conditions range from the self-limiting hepatic right upper quadrant syndrome (hepatic crisis) to the potentially lethal intrahepatic cholestasis and acute hepatic sequestration syndromes. Few cases have been documented, and there have not been many sizable studies on acute hepatic sequestration in sickle cell disease. This case is useful for clinicians who are not familiar with the intrahepatic vaso-occlusive syndromes in sickle cell disease. It provides insight into the presentation, diagnosis, and management of these syndromes.

Key words: sickle cell anemia ■ acute hepatic sequestration ■ hepatic right upper quadrant syndrome ■ partial red blood cell exchange transfusion ■ hepatomegaly ■ intrahepatic cholestasis

A 29-year-old black male presented to the emergency room with a complaint of back pain, chest pain, abdominal pain, and dysuria for three days. He had associated fever, chills, and dark urine. On presentation, his temperature was 40°C, the pulse was 120 beats per minute, and the respiratory rate was 32 breaths per minute. The blood pressure was 114/52, and his oxygen saturation was 89% while breathing room air. His physical examination revealed jaundiced skin, scleral icterus, tachycardia, right upper quadrant tenderness on palpation, a liver span 16 cm to percussion, and costovertebral angle tenderness bilaterally. His past medical history included sickle cell disease, tuberculosis with completed treatment in 2000, and a positive hepatitis-B core antibody in March of 2001. His social history included smoking one pack of cigarettes daily and occasional marijuana use, but he denied any intravenous drug or alcohol use. His blood chemistry values were total bilirubin of 49.8 mg/dl, direct bilirubin 28.5, indirect bilirubin 21.3, and an ammonia level of 81 μmol/L. The levels of urea nitrogen, creatinine, glucose, calcium, phosphorus, and electrolytes were normal. The enzymes showed an alkaline phosphatase (ImU/ml) 276, lactate dehydrogenase (U/liter) 477, gamma-glutamyl transferase (U/liter) 524, aspartate aminotransferase (U/liter) 58, alanine aminotransferase (U/liter) 61. His coagulation studies were partial-thromboplastin time (PTT) 38.1, and an International Normalized Ratio (INR) of 1.18. His hematocrit was 17%, and he had a serum white blood cell count of 24,000 with 14% bands. His urinalysis showed bilirubin, positive nitrate, positive leukocyte esterase, and numerous red and white blood cells. His urine culture, hepatitic-C virus antibody, and urine drug screen were negative. He had positive blood cultures for *Escherichia coli.* An abdominal ultrasound showed hepatomegaly and minimal gallbladder sludge, but normal intra and extrahepatic ducts. A subsequent computed tomographic (CT) exam of the abdomen, performed without the use of contrast material, showed hepatomegaly at 20 cm without lesions, absent spleen, and no biliary dilatation.

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Hospital Course

The patient was admitted to the inpatient ward. Treatment began with intravenous normal saline and parenteral levafloxacin for his bacteremia. He received a six-unit, red blood cell partial exchange transfusion and a transfusion of three units of packed red blood cells. Lactulose was given for his elevated ammonia. After treatment, his hematocrit increased to 29%, his white blood cell count decreased to 12,000, and he remained afebrile after hospital day six. His total bilirubin decreased to 4.9 mg/dl, with a direct fraction of 2.5. The transaminases normalized after hospital day five. The patient left the hospital against medical advice (AMA) after hospital day 17, prior to receiving a liver biopsy.

Epidemiology and Clinical Features

Homozygous sickle cell anemia affects 1 in 600 African-American babies, and sickle cell trait affects 8–10% of African Americans.[3,4] Liver disease is apparently prevalent in sickle cell disease. It has been estimated that hepatic complications affect 10% of patients with sickle cell disease who are admitted to the hospital.[5,6] In an autopsy study on 70 patients with sickle cell anemia, sickle thalassemia, and sickle C disease, hepatomegaly was found in 91% of the patients.[6]

Cases have shown that it is possible that infections, fever, and pain may play a role as precipitating factors in sickle cell patients that present with an intrahepatic vaso-occlusive syndrome.[7] The right upper quadrant hepatic syndrome patient typically complains of right upper quadrant pain and fever. The clinical exam is significant for jaundice and hepatic enlargement. Serum bilirubin levels are usually less than 15 mg/dl. The plasma alanine aminotransferase and aspartate aminotransferase levels are elevated.

Sixteen cases of intrahepatic cholestasis in sickle cell disease have been reported.[8] This condition is potentially catastrophic. The clinical features include fever, right upper quadrant pain, encephalopathy, and jaundice. The laboratory values show leukocytosis, elevated lactate dehydrogenase, renal failure, elevated transaminases and prolongation of the prothrombin, and partial thromboplastin time.[8]

Acute hepatic sequestration is a rarely recognized complication of vaso-occlusive crisis. It is characterized by a presentation of right upper quadrant pain. A smooth, tender, enlarged liver is noted on physical exam.[2] The lab values show a decrease in the hemoglobin/hematocrit.[2] An increase in reticulocyte count is also seen.

Pathogenesis

The causes of hepatic failure in sickle cell disease are numerous. The sickling of red blood cells, multiple blood transfusions, cocaine use, and intravascular hemolysis have been shown to be causes of hepatic failure. The sickling of red blood cells can cause hepatic infarction by vaso-occlusion, resulting in an obstruction in sinusoidal flow. This results in sequestration of red blood cells in the liver.[9] Multiple blood transfusions on a chronic basis can lead to an excessive accumulation of iron in the parenchymal cells of the liver.[3] Iron overload may contribute to organ failure, malignancy, and a higher incidence of painful crises.[4] Cocaine use can cause hypoxic injury from cocaine-induced vasospasm and sickling.[8] Intravascular hemolysis causes excessive production of bilirubin, which exceeds hepatic clearance capacity. The elevated bilirubin levels are caused by hemolysis, ineffective erythropoiesis, and hepatocellular dysfunction.[8] Studies have shown that bone alkaline phosphatase is the major enzyme fraction contributing to the increase in serum alkaline phosphatase.[10]

The acute right upper quadrant syndrome is thought to be the result of sinusoidal stagnation of sickle red blood cells in the liver, resulting in a decrease in circulation through hepatic sinusoids.

The pathophysiology of intrahepatic cholestasis is a result of sickled red blood cells plugging the hepatic sinusoids, causing vascular stasis and local hypoxia. Kupfer cell hypertrophy develops and the canaliculi become plugged with bile.[11]

Acute hepatic sequestration is believed to be caused by the obstruction of sinusoidal flow by masses of sickled erythrocytes, trapping of red blood cells within the liver, and compression of the biliary tree. This complication may have a similar basis to the splenic sequestration and the sickle lung syndromes.[12]

Diagnosis

The diagnosis of hepatic vaso-occlusive syndromes in sickle cell disease is based on clinical, laboratory, and imaging studies.[8] In the past, a liver biopsy was needed to make the diagnosis. However, a recent U.K. study conducted by the Institute of Liver Studies and the Department of Hematological Medicine reported that hepatic disease complicated by sickle cell anemia is a relative contraindication to a percutaneous liver biopsy.[13] They reported serious hemorrhage in 36% and death in 28% of sickle cell patients in hepatic crisis that underwent a percutaneous liver biopsy.[13]

Therapy

Intravenous hydration and proper analgesia are the initial treatments in sickle cell crisis. Acute hepatic right upper quadrant syndrome is managed conservatively with supportive care. However, it is important to administer a partial red blood cell exchange transfusion early in the treatment of intrahepatic cholestasis or acute hepatic sequestration.

Partial red blood cell transfusions with fresh frozen plasma have shown to help improve hepatic and renal function in intrahepatic cholestasis.[8] Simple red blood cell transfusions may result in hyperviscosity syndrome, which may result in volume overload, heart failure, intracerebral hemorrhage, and death in patients with acute hepatic sequestration.[2,8] Clinical and biological profiles improve rapidly after exchange transfusions. Red blood cell exchange transfusions decrease the amount of hemoglobin S (HbS) in circulation, resulting in an improvement in oxygen delivery and improvement in the rheologic state.[14] Hydroxyurea may be beneficial in treating sickle cell patients with chronic hepatic sequestration. A patient at St. Jude's Children's Hospital in Memphis, TN showed a resolution of his hepatomegaly and normalization of his liver volume demonstrated on serial CT studies after he was treated with hydroxyurea for 60 months.[15]

Imaging

A CT of the abdomen is the preferred diagnostic imaging study for evaluating a sickle cell patient with upper abdominal pain.[8] The CT usually shows diffuse hepatomegaly, which is caused by an expansion of the hepatic reticuloendothelial system.[8] Magnetic resonance imaging (MRI) can provide a qualitative but limited quantitative assessment of hepatic iron overload in patients whose hepatic iron levels are less than 100 μg/mg.[8] The normal values of hepatic iron in men is 200–2,000 μg/g and 200–1,600 μg/g in women.[16] An abdominal ultrasound may reveal gallstones or may show an increase in the echogenicity of the liver.[8] ^{99m}Tc hepatobiliary imaging using iminodiacetic compounds (HIDA) is reliable in confirming acute cholecystitis if the bilirubin is under 5 g/dl. Endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography provide the best means for determining the cause, location, and extent of biliary obstruction.

Differential Diagnosis of Liver Disease in Sickle Cell Patients

Sickle cell patients are prone to liver injury from viral hepatitis, iron overload, hypoxic injury, common bile duct obstruction, biliary sludge, acute cholecystitis, choledocholithiasis, and the hepatic crisis syndromes. Thus it is important to be familiar with these entities as etiologies of liver disease in sickle cell patients. Viral hepatitis is prevalent in the sickle cell population. This is due to the large quantities of blood products that this population receives. Reported rates for hepatitis B infection have ranged from 15% to 20%.[14] In the United States 1.8% of all patients with sickle cell disease are infected with the hepatitis C virus.[17,18] The progression to cirrhosis in sickle cell patients with hepatitis C is not known. There have been no American studies that have examined the prevalence of hepatitis A in sickle cell patients. Sickle cell patients should be tested for the antibodies for hepatitis A, B and C. If their serologies are negative they should receive the vaccinations for hepatitis A and B.[14]

Patients with sickle cell disease who receive blood transfusions are at risk for developing iron overload by the time they reach adulthood.[4] Measurement of serum ferritin is the most common method used to determine body iron stores. However, in sickle cell patients, interpretation of ferritin values may be complicated by changes in body iron burden. This may occur during infection, ineffective erythropoiesis, or hemolysis.[3] Studies have shown that the best way to determine iron stores in sickle cell patients is to keep accurate records of blood transfusions and serial determinations of ferritin levels in a steady state.[3,4] Desferal chelation is the only therapy that has proven to effectively treat hemochromatosis induced by red blood cell transfusions.[11] This results in an increase of urinary and biliary excretion of iron, promoting tissue recovery.[8]

Acute cholecystitis and choledocholithiasis present as right upper quadrant pain and fever in patients with sickle cell disease. Studies have estimated that 70% of patients with sickle cell disease develop gallstones.[19] Biliary sludge is detectable on an abdominal ultrasound. It may be a precursor to gallstone development. Pigmented gallstones are the most common type of gallstones seen in sickle cell patients due to chronic hemolysis. The index of suspicion for the diagnosis of acute cholecystitis, choledocholithiasis, and common bile duct obstruction can be lowered with an abdominal ultrasound or CT scan of the abdomen. Elective cholecystectomy should be considered in the treatment of sickle cell patients with symptomatic gallstones.[7] This procedure should not be performed in patients in a sickle cell pain crisis due to its high morbidity and mortality rates.

DISCUSSION

Based on the presentation and work-up, it is likely that this patient presented with acute hepatic sequestration. Acute hepatic sequestration is characterized by right upper quadrant pain and hepatomegaly. The laboratory data show hyperbilirubinemia, low hemoglobin/hematocrit with reticulocytosis. The transaminases are minimally elevated, and the CT and abdominal ultrasound show diffuse hepatomegaly.[2] Viral hepatitis was considered an unlikely culprit. It rarely causes an extensive hyperbilirubinemia, and the transaminases remain elevated for a greater time period.

Patients with sickle cell disease are prone to biliary tract disease. The lack of sonographic evidence of stones, a serum bilirubin level greater than 30 mg/

dl in the presence of normal renal function, led us away from the diagnosis of biliary tract disease. The diagnosis of right upper quadrant hepatic syndrome was excluded. In adults, the clinical course is typically three-to-seven days. The serum bilirubin levels seldom exceed 15 mg/dl, and a low hematocrit has not been described in this syndrome. Furthermore, the patient's clinical and biological profile improved rapidly after receiving the partial exchange transfusion.[2] Sickle cell intrahepatic cholestasis has a presentation similar to acute hepatic sequestration. The diagnosis of intrahepatic cholestasis was excluded based on the physical examination and laboratory data. The biochemical markers show renal failure, thrombocytopenia, and a coagulopathic state. Patients with intrahepatic cholestasis may also have an accompanying encephalopathic state.[8]

E. coli bacteremia was also excluded as a possible cause of the patient's hepatic failure. The patient's physical examination, laboratory values, and clinical course also led us away from this diagnosis. Patients with hepatic dysfunction due to *E. coli* bacteremia present with clinical indicators of septic shock. These include hypotension, encephalopathy, oliguria, renal dysfunction, metabolic acidosis, and thrombocytopenia. The transaminases are elevated with an accompanying coagulopathy. The patient did not have signs of multiorgan dysfunction. The role of the *E. coli* bacteremia in this patient's sickle cell crisis is unclear. Cases have shown that viral and bacterial infections may play a role as a precipitating factor in vaso-occlusive crises. The patient had a negative urine culture and showed no clinical signs of a secondary infection, such as an abscess or skin lesion that could have been seeded. *E. coli* may be found in the biliary tree, but it is of no consequence unless an obstruction is present.[17] *E. coli* is endogenous to the gastrointestinal tract, and it is possible that due to the patient's underlying sullen immune system, this may have precipitated the crisis.

Normal Laboratory Values

Lactate Dehydrogenase	45–90 (U/liter)
Gamma-glutamyl transferase	8–38 (U/liter)
Aspartate aminotransferase	8–20 (U/liter)
Alkaline phosphatase	30–85 (ImU/ml)
Alanine aminotransferase	5–35 (U/liter)
Total bilirubin	0.1–1.0 (mg/dl)
Indirect bilirubin	0.2–0.8 (mg/dl)
Direct bilirubin	0.1–0.3 (mg/dl)
Ammonia	47–65 (μmol/L)

CONCLUSION

Hepatic disease is common in sickle cell disease. The intrahepatic vaso-occlusive disorders seen in sickle cell disease encompass a variety of syndromes that are not often seen in a sickle cell crisis. The courses vary between a self-limiting syndrome that remits with intravenous hydration and analgesia to death from bleeding and liver failure. It can arise from a variety of insults to the liver, including ischemia, vascular occlusion, and sequestration. This case is important because acute hepatic sequestration in sickle cell disease is a manifestation of the disease that is unfamiliar to many clinicians. When it arises, it puts clinicians in a potential quandary. It is important to recognize the self-limiting hepatic right upper quadrant syndrome and the potentially lethal intrahepatic crisis and acute hepatic sequestration syndromes. Most clinicians are inclined to initially treat the more severe forms of this syndrome with simple blood transfusions, which may lead to hyperviscosity syndrome.[4] A more prudent option is to perform a partial red blood cell exchange transfusion, prior to a red blood cell transfusion. The partial red blood cell exchange transfusion will reduce the number of sickled cells and increase the hemoglobin and hematocrit.

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